cDNA Sequence of human IBR

Two alternative 5' ends:

1 TTGAGGAACAGGCAGACTCCACAGCTCCCGCCAGGAGAA

2 AAGGAAGGAGGGAGAAGGGAAGGAGTGAAGGAAGGAGTGAAA

Common Sequence:

AGGGGAGTCTACACCCTGTGGAGCTCAAGATGGTCCTGAGTGGGGCGCTGTGCTTCCGAA 60

TGAAGGACTCGGCATTGAAGGTGCTTTATCTGCATAATAACCAGCTTCTAGCTGGAGGGC 120

TGCATGCAGGGAAGGTCATTAAAGGTGAAGAGATCAGCGTGGTCCCCAATCGGTGGCTGG 180

ATGCCAGCCTGTCCCCCGTCATCCTGGGTGTCCAGGGTGGAAGCCAGTGCCTGTCATGTG 240

GGGTGGGGCAGGAGCCGACTCTAACACTAGAGCCAGTGAACATCATGGAGCTCTATCTTG 300

GTGCCAAGGAATCCAAGAGCTTCACCTTCTACCGGCGGGACATGGGGCTCACCTCCAGCT 360

TCGAGTCGGCTGCCTACCCGGGCTGGTTCCTGTGCACGGTGCCTGAAGCCGATCAGCCTG 420

TCAGACTCACCCAGCTTCCCGAGAATGGTGGCTGGAATGCCCCCATCACAGACTTCTACT 480

TCCAGCAGTGTGACTAGGGCAACGTGCCCCCCCAGAACTCCCTGGGCAGAGCCAGCTCGG 540

GTGAGGGGTGAGTGGAGGAGACCCATGGCGGACAATCACTCTTTCTGCTCTCAGGACCCC 600

CAGGTCTGACTTAGTGGGCACCTGACCACTTTGTCTTCTGGTTCCCAGTTTGCATAAATT 660

CTGAGATTTGGAGCTCAGTCCAGGGTCCTCCCCCACTGGATGGTGCTACTGCTGTGGAAC 720

CTTGTAAAAACCATGTGGGGTAAACTGGGAATAACATGAAAAGATTTCTGTGGGGGTGGG 780

GTGGGGGAGTGCTGGGAATCATTCCTGCTTAATGGTAACTGACAAGTGTTACCCTGAGCC 840

CCGCAGGCCAACCCATCCCCAGTTGAGCCTTATAGGGTCAGTAGCTCTCCACATGAAGTC 900

CTCTCACTCACCACTGTGCAGGAGAGGGAGGTGGTCATAGAGTCAGGGATCTATGGCCCT 960

TGGCCCAGCCCCACCCCCTTCCCTTTATCCTGCCACTGTCATATGCTACCTTTCCTATCT 1020

CTTCCCTCATCATCTTGTTGTGGGCATGAGGAGGTGGTGATGTCAGAAGAAATGGTTCGA 1080

GCTCAGAAGATAAAAGATAAGTAGGGTATGCTGATCCTCTTTTAAAAACCCAAGATACAA 1140

TCAAAATCCCAGATGCTGGTCTCTATTCCCATGAAAAAGTGCTCATGACATATTGAGAAG 1200

ACCTACTTACAAAGTGGCATATATTGCAATTTATTTTAATTAAAAGATACCTATTTATAT 1260

ATTTCTTTATAGAAAAAAGTCTGGAAGAGTTTACTTCAATTGTAGCAATGTCAGGGTGGT 1320

GGCAGTATAGGTGATTTTTCTTTTAATTCTGTTAATTTATCTGTATTTCCTAATTTTTCT 1380

ACAATGAAGATGAATTCCTTGTATAAAAATAAGAAAAGAAATTAATCTTGAGGTAAGCAG 1440

FIG. 1

Figure 1

AGCAGACATCATCTCTGATTGTCCTCAGCCTCCAATTCCCCAGAGTAAATTCAAATTGAA 1500

TCGAGCTCTGCTGCTCTGGTTGGTTGTAGTAGTGATCAGGAAACAGATCTCAGCAAAGCC 1560

ACTGAGGAGGAGGCTGTGCTGAGTTTGTGTGGCTGGAATCTCTGGGTAAGGAACTTAAAG 1620

AACAAAAATCATCTGGTAATTCTTTCCTAGAAGGATCACAGCCCCTGGGATTCCAAGGCA 1680

TTGGATCCAGTCTCTAAGAAGGCTGCTGTACTGGTTGAATTGTGTCCCCCTCAAATTCAC 1740

ATCCTTCTTGGAATCTCAGTCTGTGAGTTTATTTGGAGATAAGGTCTCTGCAGATGTAGT 1800

TAGTTAAGACAAGGTCATGCTGGATGAAGGTAGACCTAAATTCAATATGACTGGTTTCCT 1860

TGTATGAAAAGGAGAGGACACAGAGACAGAGGAGACGCGGGGAAGACTATGTAAAGATGA 1920

AGGCAGAGATCGGAGTTTTGCAGCCACAAGCTAAGAAACACCAAGGATTGTGGCAACCAT 1980

CAGAAGCTTGGAAGAGGCAAAGAAGAATTCTTCCCTAGAGGCTTTAGAGGGATAACGGCT 2040

CTGCTGAAACCTTAATCTCAGACTTCCAGCCTCCTGAACGAAGAAAGAATAAATTTCGGC 2100

TGTTTTAAGCCACCAAGGATAATTGGTTACAGCAGCTCTAGGAAACTAATACAGCTGCTA 2160

AAATGATCCCTGTCTCCTCGTGTTTACATTCTGTGTGTGTCCCCTCCCACAATGTACCAA 2220

AGTTGTCTTTGTGACCCAATAGAATATGGCAGAAGTGATGGCATGCCACTTCCAAGATTA 2280

GGTTATAAAAGACACTGCAGCTTCTACTTGAGCCCTCTCTCTCTGCCACCCACCGCCCCC 2340

AATCTATCTTGGCTCACTCGCTCTGGGGGAAGCTAGCTGCCATGCTATGAGCAGGCCTAT 2400

AAAGAGACTTACGTGGTAAAAAATGAAGTCTCCTGCCCACAGCCACATTAGTGAACCTAG 2460

AAGCAGAGACTCTGTGAGATAATCGATGTTTGTTGTTTTAAGTTGCTCAGTTTTGGTCTA 2520

ACTTGTTATGCAGCAATAGATAAATAATATGCAGAGAAAGAG(A_n) 2562

cDNA Sequence of murine IBR

GGCACGAGGGGAGCCTGCTTTCTACTTAGGTCTCAAATTTTCCAGCCTTGTCTTTGCCTA 60

AAATTTCCTGCTGTTTATTTCAAAATAGGGTCTACATACTGTGGAGCTCATGATGGTTCT 120

GAGTGGGGCACTATGCTTCCGAATGAAGGATTCAGCCTTGAAGGTACTGTATCTGCACAA 180

TAACCAGCTGCTGGCTGGAGGACTGCACGCAGAGAAGGTCATTAAAGGTGAGGAGATCAG 240

TGTTGTCCCAAATCGGGCACTGGATGCCAGTCTGTCCCCTGTCATCCTGGGCGTTCAAGG 300

AGGAAGCCAGTGCCTATCTTGTGGGACAGAGAAAGGGCCAATTCTGAAACTTGAGCCAGT 360

GAACATCATGGAGCTCTACCTCGGGGCCAAGGAATCAAAGAGCTTCACCTTCTACCGGCG 420

GGATATGGGTCTTACCTCCAGCTTCGAATCCGCTGCCTACCCAGGCTGGTTCCTCTGCAC 480

CTCACCGGAAGCTGACCAGCCTGTCAGGCTCACTCAGATCCCTGAGGACCCCGCCTGGGA 540

TGCTCCCATCACAGACTTCTACTTTCAGCAGTGTGACTAGGGCTGCGTGGTCCCCAAAAC 600

TCCATAAGCAGAGGCAGAGTAGGCAGTGGCGGCTCCTGATAGAGGATAGAGAGACAGAGG 660

AGCTCCACAGTAGGTGGCTTACTCCTCTCCTTCCCTACTGGACTCCCGCTTCTGACCTAA 720

GGCACACAGACACTCTCTTCTCCTGCATCCCAGTGCTGGTAAATCTTCTGGTATTTGGAG 780

CTCAATGTGTAGATTCTTTCAGATTGGATGGTACTACCTCTGGTGTGGAACCCAATAGAA 840

ACCACGTAGGACCAACAAAGAGCAACATAAAAGATTCTTGGGTGAAGAAGAGGTGGGAAC 900

TGTTCATACATAGTAAGATCTGACACAGTACCTCAGAAGTCCTGCCATTCCTTATGTTCT 960

GGAGAAAGTGGAGGGGGGGTCACCAAGACTTTCTCTGGCTGGCTGGGCCCTTTCCCTCAA 1020

CCTTTCTGACATCTGCAGCCTCTCTCATTCTTGCCTTCATTCTCTGGCCCTGAACCGAGA 1080

GGGTGATATCAGGATAGCTGACAGAAGATGACCAGGCACACTGTCCTGGTTTGAAACCAG 1140

AGGGGACAATAAAAAACCCTGATTCTGGTCTCTACTCACATAAAAAGAAGCTTGTGAACA 1200

TTAAGTGGGAAGAGATTGCTACTAAATAACATACCTTGTAATTTCATCTTAATTAAAATA 1260

TACTTCTCTATATTATATATTTTA$_{(n)}$ 1284

FIG. 2

IBR Polypeptides

(A) Human IBR polypeptide

MVLSGALCFR MKDSALKVLY LHNNQLLAGG LHAGKVIKGE EISVVPNRWL
DASLSPVILG VQGGSQCLSC GVGQEPTLTL EPVNIMELYL GAKESKSFTF
YRRDMGLTSS FESAAYPGWF LCTVPEADQP VRLTQLPENG GWNAPITDFY
FQQCD

(B) Mouse IBR polypeptide

MVLSGALCFR MKDSALKVLY LHNNQLLAGG LHAEKVIKGE EISVVPNRAL
DASLSPVILG VQGGSQCLSC GTEKGPILKL EPVNIMELYL GAKESKSFTF
YRRDMGLTSS FESAAYPGWF LCTSPEADQP VRLTQIPEDP AWDAPITDFY
FQQCD

FIG. 3

Comparison of Human and Mouse IBR Polypeptide Sequences

```
mIBR: 1    MVLSGALCFRMKDSALKVLYLHNNQLLAGGLHAEKVIKGEEISVVPNRALDASLSPVILG 60
           MVLSGALCFRMKDSALKVLYLHNNQLLAGGLHA KVIKGEEISVVPNR-LDASLSPVILG IBRcon.
hIBR: 1    MVLSGALCFRMKDSALKVLYLHNNQLLAGGLHAGKVIKGEEISVVPNRWLDASLSPVILG 60

mIBR: 61   VQGGSQCLSCGTEKGPILKLEPVNIMELYLGAKESKSFTFYRRDMGLTSSFESAAYPGWF 120
           VQGGSQCLSCG--+-P+L-LEPVNIMELYLGAKESKSFTFYRRDMGLTSSFESAAYPGWF IBRcon.
hIBR: 61   VQGGSQCLSCGVGQEPTLTLEPVNIMELYLGAKESKSFTFYRRDMGLTSSFESAAYPGWF 120

mIBR: 121  LCTSPEADQPVRLTQIPEDPAWDAPITDFYFQQCD 155
           LCT-PEADQPVRLTQ+PE+--W+APITDFYFQQCD IBRcon.
hIBR: 121  LCTVPEADQPVRLTQLPENGGWNAPITDFYFQQCD 155
```

FIG. 4

Comparison of Human IBR and pro-IL-1ra Polypeptide Sequences

```
hIL-1ra: 38   FRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVP-------IEPHALFLGIHGGKM 90
              FR+ D   K  YL NNQL+AG L    V   E+I VVP       + P   + LG+ GG  con.
hIBR   : 9    FRMKDSALKVLYLHNNQLLAGGLHAGKVIKGEEISVVPNRWLDASLSP--VILGVQGGSQ 66

hIL-1ra: 91   CLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAACPGWFLCTAM 150
              CLSC   G E   L LE VNI +L      K+ K F F R D G T+SFESAA PGWFLCT   con.
hIBR   : 67   CLSC-GVGQEPTLTLEPVNIMELYLGAKESKSFTFYRRDMGLTSSFESAAYPGWFLCTVP 125

hIL-1ra: 151  EADQPVSLTNMPDEG---VMVTKFYFQE 175
              EADQPV LT +P+ G     +T FYFQ+ con.
hIBR   : 126  EADQPVRLTQLPENGGWNAPITDFYFQQ 153
```

FIG. 5

Recombinant IBR Polypeptides

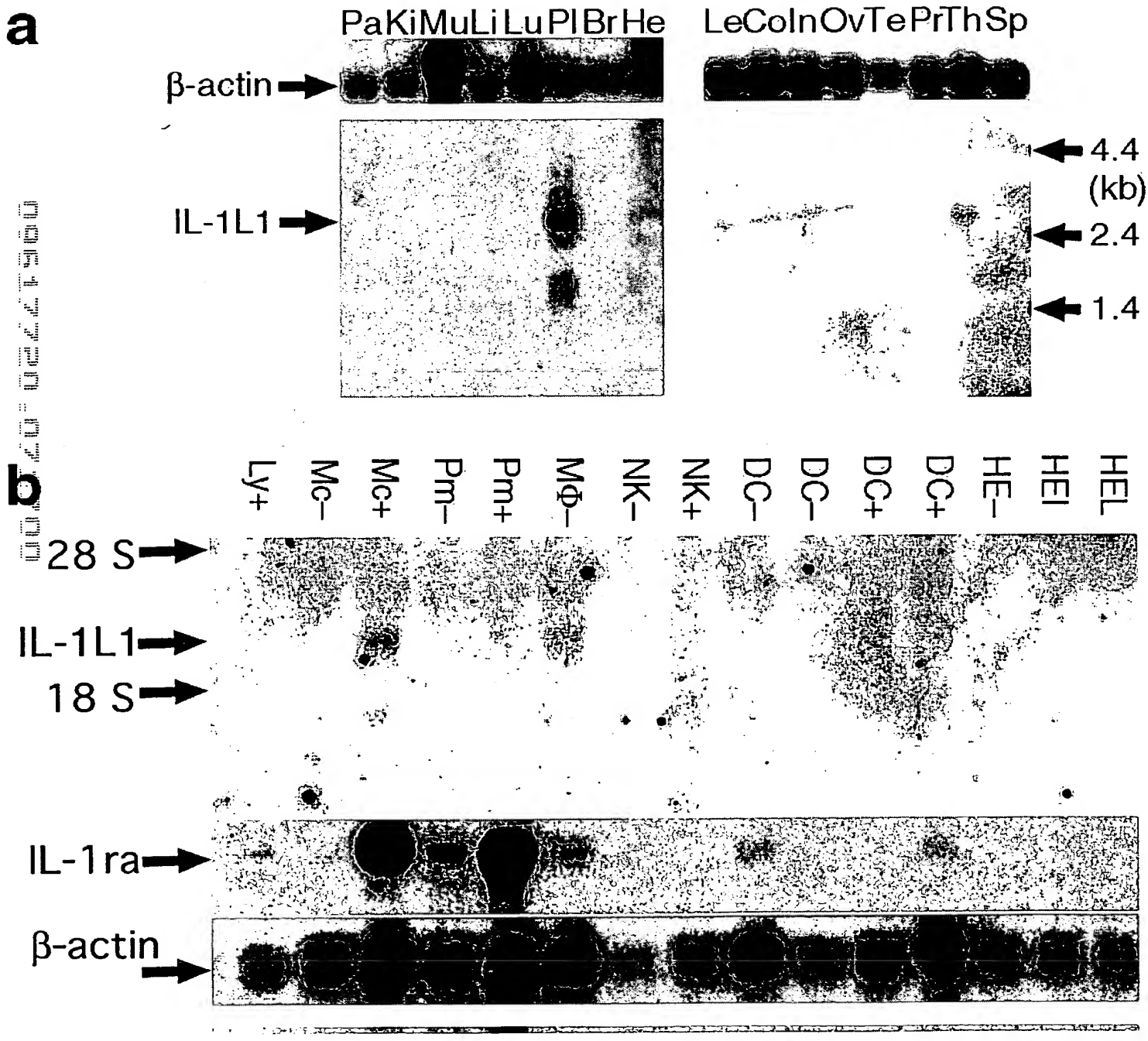
MVLSGALCFR MKDSALKVLY LHNNQLLAGG LHAGKVIKGE EISVVPNRWL
DASLSPVILG VQGGSQCLSC GVGQEPTLTL EPVNIMELYL GAKESKSFTF
YRRDMGLTSS FESAAYPGWF LCTVPEADQP VRLTQLPENG GWNAPITDFY
FQQCD

VLSGALCFR MKDSALKVLY LHNNQLLAGG LHAGKVIKGE EISVVPNRWL
DASLSPVILG VQGGSQCLSC GVGQEPTLTL EPVNIMELYL GAKESKSFTF
YRRDMGLTSS FESAAYPGWF LCTVPEADQP VRLTQLPENG GWNAPITDFY
FQQCD

GSSVLSGALCFR MKDSALKVLY LHNNQLLAGG LHAGKVIKGE EISVVPNRWL
DASLSPVILG VQGGSQCLSC GVGQEPTLTL EPVNIMELYL GAKESKSFTF
YRRDMGLTSS FESAAYPGWF LCTVPEADQP VRLTQLPENG GWNAPITDFY
FQQCD

FIG. 6

FIG. 7


a
Pa Ki Mu Li Lu Pl Br He
Le Co In Ov Te Pr Th Sp
β-actin
IL-1L1
4.4
(kb)
2.4
1.4
b
Ly+
Mc−
Mc+
Pm−
Pm+
Mφ−
NK−
NK+
DC−
DC−
DC+
DC+
HE−
HEI
HEL
28 S
IL-1L1
18 S
IL-1ra
β-actin

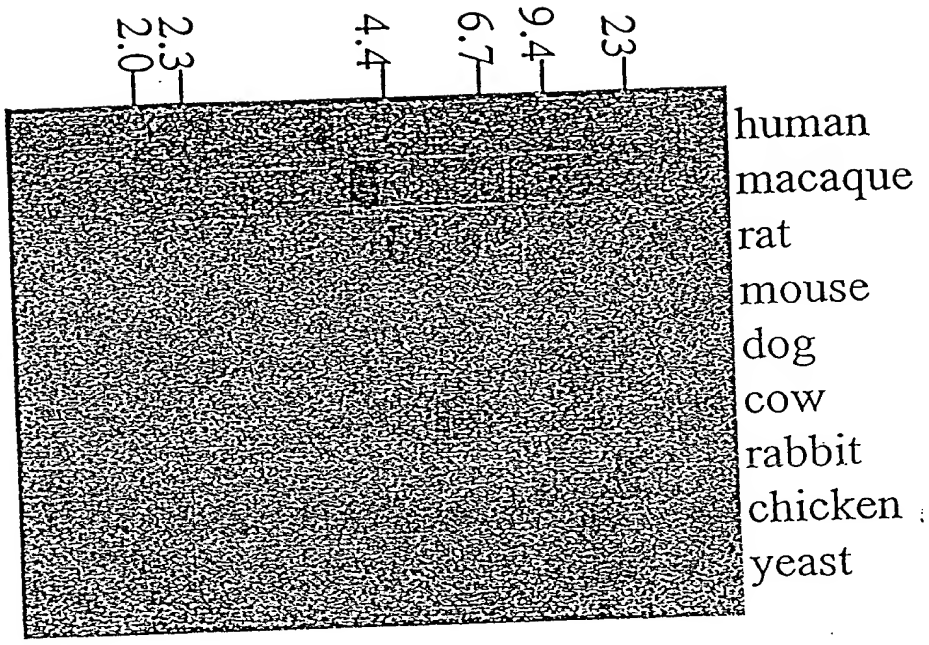

2.3
2.0
4.4
6.7
9.4
23
human
macaque
rat
mouse
dog
cow
rabbit
chicken
yeast

FIG. 8

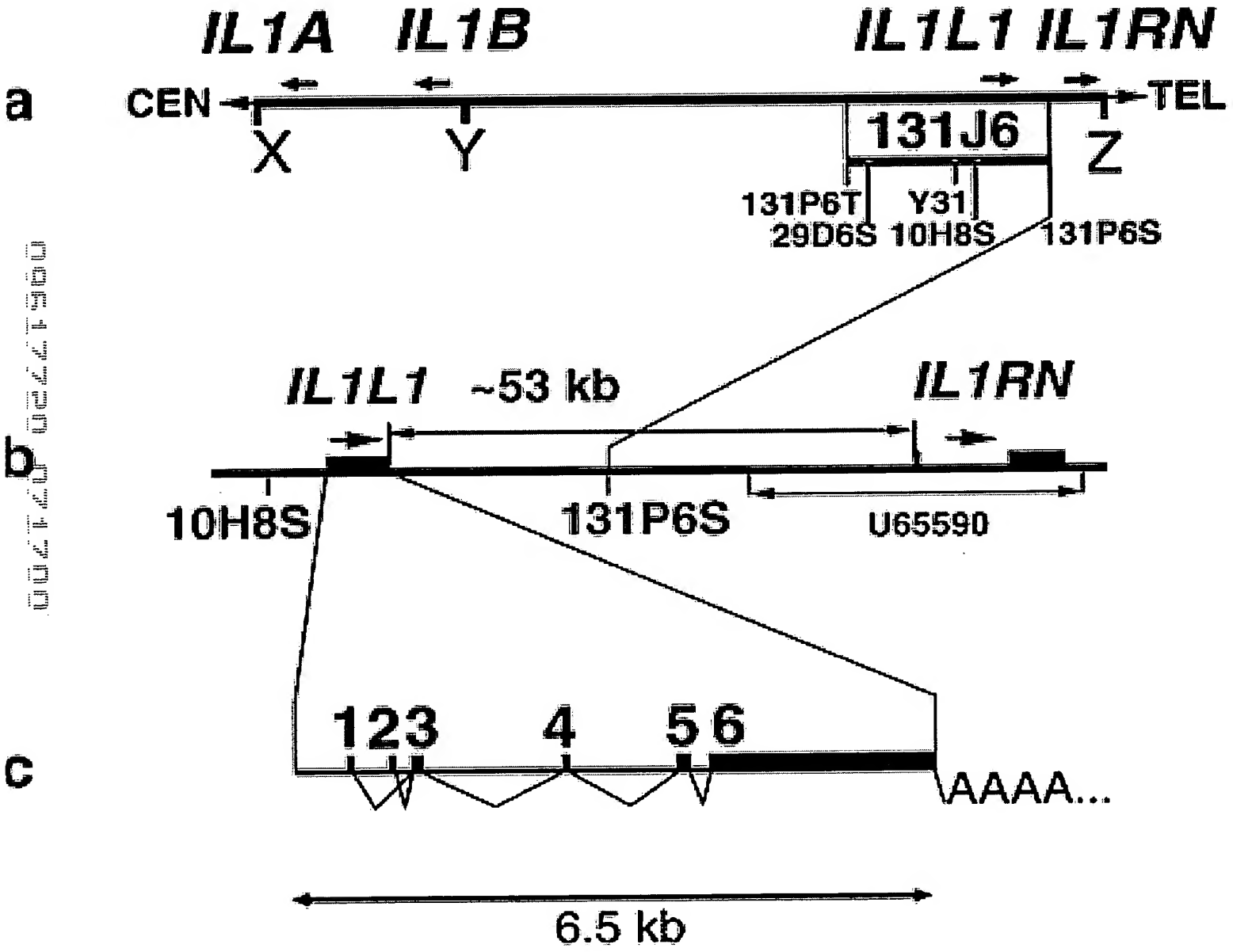

IL1A
IL1B
IL1L1
IL1RN
a
CEN
TEL
X
Y
131J6
Z
131P6T
Y31
29D6S
10H8S
131P6S
IL1L1
~53 kb
IL1RN
b
10H8S
131P6S
U65590
1 2 3
4
5 6
c
AAAA...
6.5 kb

FIG. 9

a

```
cDNA SEQUENCES CONTAINING EXON 1
CTGGCAATGGCAGGCAGGAAAGACAGAGGAAGGAAGGAGGGAGAAGGGAAGGAGTGAAGGAAGGAGTGAAAAA// exon 3
^                  ^
-74'   M  A  G  R  K  D  R  G  R  K  E  G  E  G  K  E ***         ***

cDNA SEQUENCES CONTAINING EXON 2
TTGGAGGAACAGGCAGACTCCACAGCTCCCGCCAGGAGAAAGGAACATTCTGAG// exon 3
^                    ^          ^   ^
-54                             ^
```

b

5′ flank	start	exon	start seq	cDNA	end seq	end	3′flank
	+ 451	1	CTGGCAATGG	-74′- -1′	AGTGAAAAAG	+ 524	gtaaggaaga
	+ 969	2	TTGGAGGAAC	-54 - -1	ACATTCTGAG	+1022	gtatgctctg
tccaaaatag	+1193	3	GGGAGTCTAC	1 - 56	TGTGCTTCCG	+1248	gtgagtgtat
gatgtttcag	+2631	4	AATGAAGGAC	57 - 142	GTCATTAAAG	+2716	gttggtgatg
tttcccacag	+3905	5	GTGAAGAGAT	143 - 270	AACACTAGAG	+4032	gtgagacttg
ctgccggcag	+4234	6	CCAGTGAACA	271 - 2559	AGAGAAAGAG	+6522	aaacaaatgc

c

```
IL-1L1    MVLSGALCFR(2)MKDSALKVLYLHNNQLLAGGLHAGKVIKG(1)EEISVVPNRWLDASLSP
IL-1ra ..RKSSKMQAFR(2)IWDVNQKTFYLRNNQLVAGYLQGPNVNLEE(1)KIDVVP-----IEPHA

IL-1L1    VILGVQGGSQCLSCG-VGQEPTLTLE(3)VNIMELYLGAKESKSFTFYRRDM..
IL-1ra    LFLGIHGGKMCLSCVKSGDETRLQLE(3)VNITDLSENRKQDKRFAFIRSDS..
```

FIG. 10

FIG. 11

1 CATGAGCAAA GATGTTAATA CAAAGATGTT TGTCACAACA TGGTTTTCAA TAGCAAAAAA

61 AGAGAGAAAA ATATATAAAA GACAAATAAC AGTGGATAGG TTTCAATAAA TAATGTTACA

121 GTGATACAGT TAAATACTAT ACAGCTATTG AAGCATGTCA TTATTCATAT TTAGTATGGA

181 AAGATATTTT GCTATTTTGC TACATGAAAA AATGAGGTTG GAAAAAGTAT AGGTTTTGTG

241 AATCTGTTGT ATGAAAGCTG TCTATAGTTA CATGTGTATG TGTGTGGAGG AAAAAGTGTT

301 GTCATTGGTT TTCTGATGAT GCACTCAGAA AAGACAAGTA TTCACATTTT TTCTTGTGGC

361 TGATCTGGAT TTTCAGGTTT TTCTACAATG AACATGTAGG CTGAACATTC CCTAAGCAGG

421 AGAGTCCCAC CTCTAACATC TCCTGTAGGC CTGGCAATGG CAGGCAGGAA AGACAGAGGA

481 AGGAAGGAGG GAGAAGGGAA GGAGTGAAGG AAGGAGTGAA AAAGGTAAGG AAGAAAGGGA

541 ATAGGGGAGG AAGGGAGGAA ATGGGAAGGG AAAGAAGGAA AGGAAGGAAA GAGGGAGGGA

601 AGAAAGGAAG GGAAAAGGGA GGGAGTGAGT GAATGAAAGA TGGAAAGAAG GAAGAAAGGG

661 AGGGAGGCAG GGAGGAAAGA AAGTTGCGCT TCCCTTGAGC TGCCATGGGC ACTGACTCTT

721 AGGGTCTGAA AGCCCCTGAG ATGCAAAAGC CTAGTGCTCA CAAAGAGCTG GAAAGCCTCA

781 AGGAAGTTCT TCAATATTTC TGGAAGGAAA CTGTCTCCAG AAGCTTCCCT CCCCACGACA

841 GATAATGAGC AGCAAGTGCT TCTGGCGACT TAGGGTGATG TGAAATCACG CTGGGAATCC

901 TGCTCCTCCT CAGGTCCTGG CAGTTTCAGG GCCCCTCCCT AGGCCTTACT TAAAAGGCTG

961 AGGCATCCTT GGAGGAACAG GCAGACTCCA CAGCTCCCGC CAGGAGAAAG GAACATTCTG

1021 AGGTATGCTC TGGGGCGCTG GTGGTACCGG AGCTCTCTCC TGACCCCAGA CCCAGAATCT

1081 GCTCCGTGGA GGCTGTTCAC ATGCTGGGGA GCTCGGTGCA GCTGCTTGCT CCCCAGACCC

1141 CAGCCAACTC AGCCTCTCTC TCCATGATTT TCTGTTGTTT ATTCCAAAAT AGGGGAGTCT

1201 ACACCCTGTG GAGCTCAAGA TGGTCCTGAG TGGGGCGCTG TGCTTCCGGT GAGTGTATGA

1261 GGCCCTGGTT TGGTGGTGTC CTCCGGAGGA AGTGAGTTCT GGATAGACCC GTTGTCCAGC

1321 TCTGAGCAGG AGGGAGGAAG GGAGGGGCTG CCATTGCAGC TGGGAAATTG TGACCAGCAC

1381 CTCATTGCTC TTAGAGTTTT CCCAGCCTTT TTCAAATAGG GGCAGGACTG GGGCAGGCCA

1441 TCTCACAAGG GGTCCCTGAT GCTGAGGGGG ACAAGTGAAC CTCCCAGTCT AGAGCTCCAG

1501 CCAAGTCTAT CCAAGGTGGG AACGGGGGCC AGGATCCCTG CTCAGAGCTC CGCCATTGTC

1561 CCCCATCACA GTGAATGGAT GTAAGCTCAC CCACTCTGTG CCCCTACCTC CCTGCTACTC

1621 TTTGGGGATA ATAATAAAAC AAAAACCATT ACCATCAGCC AGTCTGTCCA CCCACTGGCA

1681 TGTACCAAGC CAGACACTCT GCCGTGTTCT GGGCTTAACA ACAGAGGATG AGAGTGGTCC

1741 TTTCTCTCAG TCTAATAAAG CACTTCCCAC GATGTGTTCT ATGGGACTCG ATTAGAGGAG

1801 TCCCACAGAG GCATCCAGGA GATGCTTTAC ACAGTGGAGC TCTCTGATCA AGTAAATGCA

1861 GGGAATTCTG CTTTCTACAT CCTCTCATAA GAGAACCACA GCCCAGCTCA GCATATGAGT

1921 GACTGAGGTT TTCTGAAGTA AGGCAACTTG TTGAATCGTA TTTAGCTATG CATCGACCCA

1981 ATTTTTACAC TGCATCCTTT TCCCCCATAT AACTTTTGGA GAAACCCACT TTAGGATACA

2041 TCTTCCACCT CATAGGATGC CAGGAAATCA ACTGAGTTCA AAGATGAGAA ACAACTTTGA

2101 AAAGTTAAAT AAAAGAAATT TAAATTTAAA GAAACTCCTC ACTTAGTAAG GAATATATGA

2161 CCAAATAGAA ATACATGTAT CTTGAAGAAT TGAAGAATCA GGCTTTAACG TGGAAGAGGC

2221 CTGGATGTTA TCCAACCCAT CATCTTAGTG TAGCAATGGG GAGGCTCAGG CCCAGAGTGG

2281 GCGAGAGAGT TGTCTCCTGC GACTCAGCAG CATTGGAGGC ATAGATGGGG CAAGAACCTA

2341 GGGCTCTGAC TCACCGTGCA GCTTCTCTTC CAACAGGAGA TGGGTTGGGG CAGAAAAGGT

2401 TGAATAGGGT GAAGGAGCAA ACCACAGACT CCAGTGGGAG ACTGTGGGGT CATCCTCCTT

2461 GTAGGGCATG AGCCCAGCAG GGCTGGGAGA CAAGGCTGTG CTGTTACTTC TGGCACAGTA

2521 GGAAGAAAGA GAGACAAAAT GCCTGAGATC AGGGGGTTCT CTGGATCCAG GGCATGCTGG

2581 AGTGTCCACC CTCCTCCTAA TGTAGTCCTC ACCCCTTCCT GATGTTTCAG AATGAAGGAC

2641 TCGGCATTGA AGGTGCTTTA TCTGCATAAT AACCAGCTTC TAGCTGGAGG GCTGCATGCA

2701 GGGAAGGTCA TTAAAGGTTG GTGATGAAAC ATGACCCACT TTCCTTGGTC TCTATACACT

2761 CTCAGGGGAG GGGGCCTGAA GAGGGCTTAG AATAGTCATA CAGATTAGCA TAGGCCTACA

2821 GAGCCCAGGC ATTAGGGCAG CACAAACCAG GCTCTAAGCA AAGGCAAATA AAATACTACA

2881 CCTCTCAGCA AAGTGAAGAC ACACGCTCTG GGGCCACCTG AAGCTTCTGT GCAGAAGTGA

2941 GAATGTTTTC CAAGAGGCTT GTCTTGTCAT TCCCTTACAG GTAGATTTAG GTCAAGCATT

3001 GCATTCCCTG GGAGCCAGTA AGTACCAAGG AGAGAACTAA CGTAGATTCT CTATACCTTT

3061 TTTCCCATAT GGGAGTGGGT TTCTGCCTCT CCACCCTGGG TCCCCTCTGC TCTCTGAAGA

3121 TCCTCAGTCA CTTAGAGTGG AGGGACCCAG AGAACAGGTG GCATTGTTGG ACCTCCTGCT

3181 TGCTCACTCT GCCCCATGCA CTGCAACAGG TCCCTCTCTA AAATAGTTTG CACCTGCCCA

3241 CCTGGGGCAC CCTTGCTGAG CACAGATGCC AGGTAGATCC TTCAGCTAGG CCATATGTGT

3301 ATGTGTGTGC TTACTGGTGT ATGTATGTGT GCATGCAGGC ATATATGTGT GAGCATATGT

3361 GTGCATGCAT GTATCTGTAT GTAACCATGT ATGTGTGAGT GCAGGTATGT AGGTATGAGC

3421 ATGTGTGTGT ATATGTATAT GTGTGCATGC ATGTATCTGT GCATGTATGT ATCTGATGTA

3481 TGTGGGTGGT GAGGGGATGT ACAGAGAGGA ATGAGACCCT CTTTTGCTCT CAGCAACCTC

3541 ACAGGGTGTA GAAAGTTGTC CAAACAATTC CAAAGGGGGG CTTATTAAGA CAGGGTTCAG

3601 AAAAAGGCCT GAGACCCAAG GGGCATTAAA GGAGGGGGTT GAGTCTATTT TGGGTTGTAG

3661 AGGCTTGAAG ATTTGACCCT GAACTAGAGG GTGGAGTGGA GGTGGTACAA TGTGCTTCCA

3721 TGCCTTGATG TCCACTCTGG GCCAGTGGAC AGGAGAAGCC ATGTCATGAC AGCTGCTGAG

3781 AAGCCTCCCT TCTGCCCAGC CTGGGGGCAG GCCGTCTCAC AGCAGTCCTG TGCCCTAGAG

3841 CCCAGGACAG GGGAAGAAGG AGGGAAAGGC ATCCAGGGCC CTGCATCTGG CCTCTTTCCC

3901 ACAGGTGAAG AGATCAGCGT GGTCCCCAAT CGGTGGCTGG ATGCCAGCCT GTCCCCCGTC

3961 ATCCTGGGTG TCCAGGGTGG AAGCCAGTGC CTGTCATGTG GGGTGGGGCA GGAGCCGACT

4021 CTAACACTAG AGGTGAGACT TGGGGCATCC TCACTGGGGA CTCAGCCACA GATGCTGAGC

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4141 GATGGCAGCT TTGCCTCCTC CCTAAGGATC CTGCCCAGCC CTCCCTCTGC CCCTGCTTCT

4201 GCCCTCACCT GACCTCCCCT CCTCTGCCGG CAGCCAGTGA ACATCATGGA GCTCTATCTT

4261 GGTGCCAAGG AATCCAAGAG CTTCACCTTC TACCGGCGGG ACATGGGGCT CACCTCCAGC

4321 TTCGAGTCGG CTGCCTACCC GGGCTGGTTC CTGTGCACGG TGCCTGAAGC CGATCAGCCT

4381 GTCAGACTCA CCCAGCTTCC CGAGAATGGT GGCTGGAATG CCCCCATCAC AGACTTCTAC

4441 TTCCAGCAGT GTGACTAGGG CAACGTGCCC CCCAGAACTC CCTGGGCAGA GCCAGCTCGG

4501 GTGAGGGGTG AGTGGAGGAG ACCCATGGCG GACAATCACT CTCTCTGCTC TCAGGACCCC

4561 CACGTCTGAC TTAGTGGGCA CCTGACCACT TTGTCTTCTG GTTCCCAGTT TGGATAAATT

4621 CTGAGATTTG GAGCTCAGTC CACGGTCCTC CCCCACTGGA TGGTGCTACT GCTGTGGAAC

4681 CTTGTAAAAA CCATGTGGGG TAAACTGGGA ATAACATGAA AAGATTTCTG TGGGGGTGGG

4741 GTGGGGGAGT GGTGGGAATC ATTCCTGCTT AATGGTAACT GACAAGTGTT ACCCTGAGCC

4801 CCGCAGGCCA ACCCATCCCC AGTTGAGCCT TATAGGGTCA GTAGCTCTCC ACATGAAGTC

4861 CTGTCACTCA CCACTGTGCA GGAGAGGGAG GTGGTCATAG AGTCAGGGAT CTATGGCCCT

4921 TGGCCCAGCC CCACCCCCTT CCCTTTAATC CTGCCACTGT CATATGCTAC CTTTCCTATC

4981 TCTTCCCTCA TCATCTTGTT GTGGGCATGA GGAGGTGGTG ATGTCAGAAG AAATGGCTCG

5041 AGCTCAGAAG ATAAAAGATA AGTAGGGTAT GCTGATCCTC TTTTAAAAAC CCAAGATACA

5101 ATCAAAATCC CAGATGCTGG TCTCTATTCC CATGAAAAAG TGCTCATGAC ATATTGAGAA

5161 GACCTACTTA CAAAGTGGCA TATATTGCAA TTTATTTTAA TTAAAAGATA CCTATTTATA

5221 TATTTCTTTA TAGAAAAAAG TCTGGAAGAG TTTACTTCAA TTGTAGCAAT GTCAGGGTGG

5281 TGGCAGTATA GGTGATTTTT CTTTTAATTC TGTTAATTTA TCTGTATTTC CTAATTTTTC

5341 TACAATGAAG ATGAATTCCT TGTATAAAAA TAAGAAAAGA AATTAATCTT GAGGTAAGCA

5401 GAGCAGACAT CATCTCTGAT TGTCCTCAGC CTCCACTTCC CCAGAGTAAA TTCAAATTGA

5461 ATCGAGCTCT GCTGCTCTGG TTGGTTGTAG TAGTGATCAG GAAACAGATC TCAGCAAAGC

5521 CACTGAGGAG GAGGCTGTGA TGAGTTTGTG TGGCTGGAAT CTCTGGGTAA GGAACTTAAA

5581 GAACAAAAAT CATCTGGTAA TTCTTTCCTA GAAGGATCAC AGCCCCTGGG ATTCCAAGGC

5641 ATTGGATCCA GTCTCTAAGA AGGCTGCTGT ACTGGTTGAA TTGTGTCCCC CTCAAATTCA

5701 CATCCTTCTT GGAATCTCAG TCTGTGAGTT TATTTGGAGA TAAGGTCTCT GCAGATGTAG

5761 TTAGTTAAGA CAAGGTCATG CTGGATGAAG GTAGACCTAA ATTCAATATG ACTGGTTTCC

5821 TTGTATGAAA AGGAGAGGAC ACAGAGACAG AGGAGACGCG GGGAAGACTA TGTAAAGATG

5881 AAGGCAGAGA TCGGAGTTTT GCAGCCACAA GCTAAGAAAC ACCAAGGATT GTGGCAACCA

5941 TCAGAAGCTT GGAAGAGGCA AAGAAGAATT CTTCCCTAGA GGCTTTAGAG GGATAACGGC

6001 TCTGCTGAAA CCTTAATCTC AGACTTCCAG CCTCCTGAAC GAAGAAAGAA TAAATTTCGG

6061 CTGTTTTAAG CCACCAAGGA TAATTGGTTA TGGCAGCTCT AGGAAACTAA TACAGCTGCT

6121 AAAATGATCC CTGTCTCCTC GTGTTTACAT TCTGTGTGTG TCCCCTCCCA CAATGTACCA

6181 AAGTTGTCTT TGTGACCAAT AGAATATGGC AGAAGTGATG GCATGCCACT TCCAAGATTA

6241 GGTTATAAAA GACACTGCAG CTTCTACTTG AGCCCTCTCT CTCTGCCACC CACCGCCCCC

6301 AATCTATCTT GGCTCACTCG CTCTGGGGGA AGCTAGCTTC CATGCTATGA GCAGGCCTAT

6361 AAAGAGACTT ATGTGGTAAA AAATGAAGTC TCCTGCCCAC AGCCACATTA GTGAACCTAG

6421 AAGCAGAGAC TCTGTGAGAT AATCAATGTT TGTTGTTTTA AGTTGCTCAG TTTTGGTCTA

6481 ACTTGTTATG CAGCAATAGA TAAATAATAT GCAGAGAAAG AGAAACAAAT GCATTTGTTT

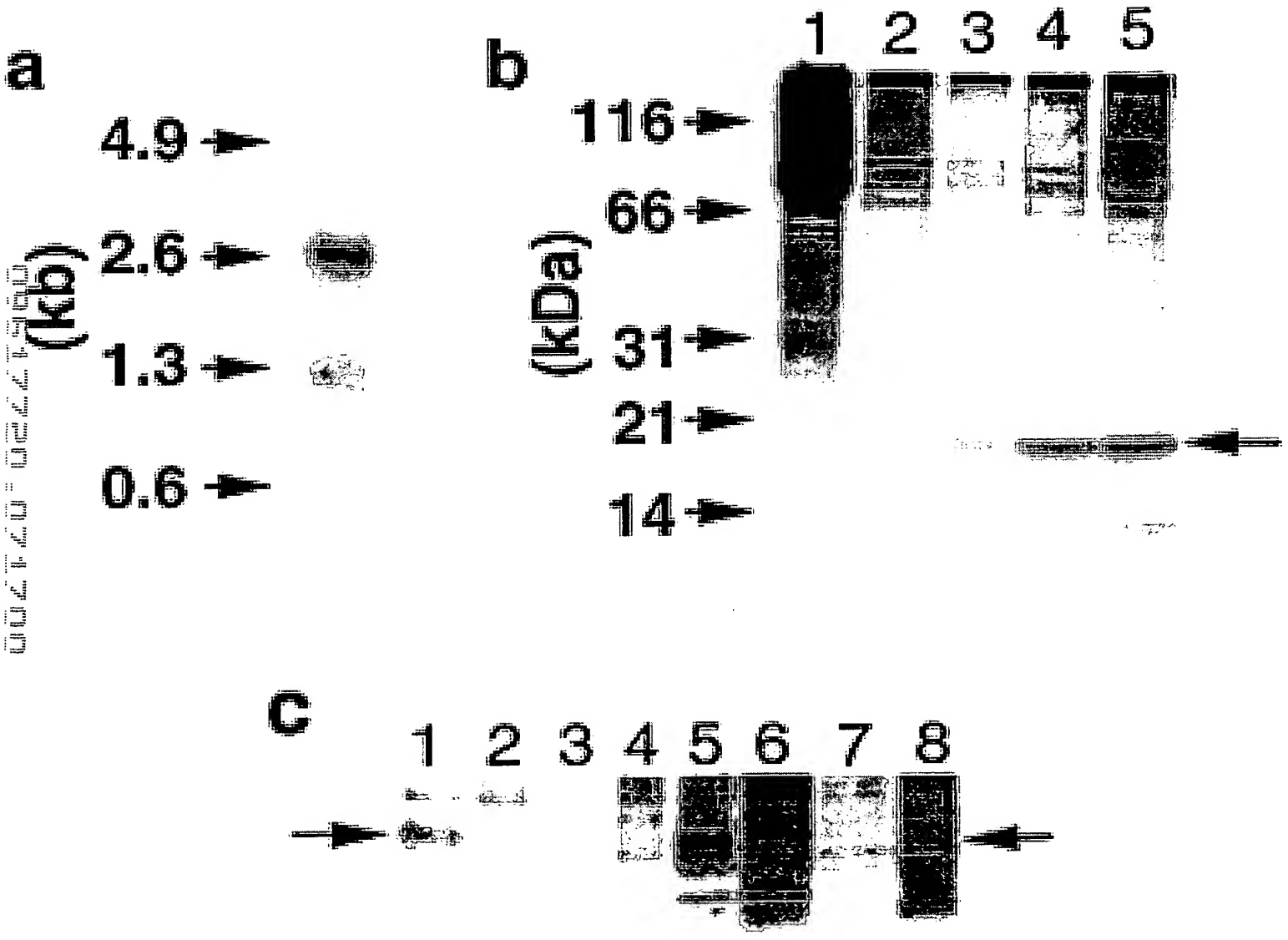

FIG. 12

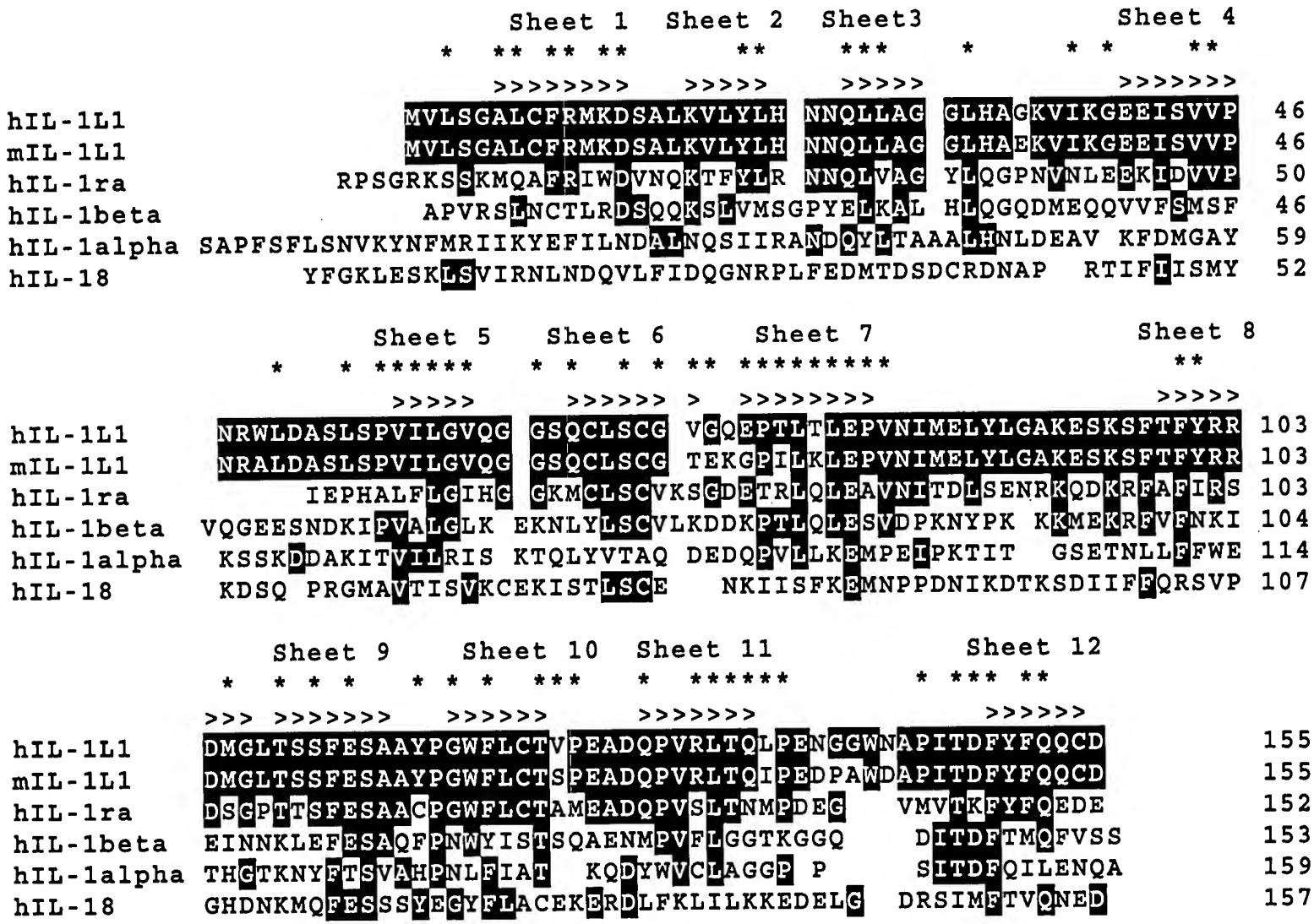

FIG. 13